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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,697	COUCH ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,16,18-21 and 24-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-16,18-21,24-29* is/are rejected.

7)☒ Claim(s) *16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13, 15-16, 18-21 and 24-29 are presented for examination.

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and submission filed November 18, 2008 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 1-13, 15-16, 18-21 and 24-29 remain pending and under examination. Claims 1, 16 and 26 are amended. Claim 14 is cancelled.

Applicant's arguments, filed November 18, 2008, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and objections are either reiterated or newly applied. They constitute the complete set of rejections and objections presently being applied to the instant application.

Applicant's Summary of the Interview Held October 15, 2008

Applicant's summary of the interview held with Examiner Royds and SPE Ardin Marschel at pgs.6 and 9 of the Remarks filed November 18, 2008 has been noted. It appears, however, that there is some confusion over what was agreed to, if anything, in the interview of October 15, 2008. Specifically, Applicant alleges that, "The written description rejection was discussed during the interview. The Applicants understand that the Examiners tentatively agreed that claims reciting a pharmaceutical combination wherein each dosage formulation releases a fixed ratio of d- to l-amphetamine may be sufficiently described in the specification." Applicant further alleges at p.9, "For the reasons stated above, the claims as amended are adequately described in the specification. Thus, this rejection should be

withdrawn. It is the Applicants understanding that Supervisory Examiner Marschel and Examiner Royds agreed during the interview that a combination comprising fixed release ratio amphetamine formulations is adequately described in the specification."

The Examiners disagree with this account of the interview, since no agreement was made as to what was or was not adequately described in the instant specification. The Examiners did agree that all rejections would be considered in light of the discussion held during the interview of October 15, 2008 and further considered in light of the remarks presented in the previous response, but did not agree to the withdrawal or obviation of any rejections. Note that the issues that were discussed during the interview with regard to the written description rejection pertained to whether the instant specification adequately described what actually accomplishes the claimed release profile, *not* whether an amendment to add that a fixed ratio of isomer is released was adequately described in the instant specification.

Objection to the Claims (New Grounds of Objection)

Claim 16 is objected to for failing to define the acronym "ADHD" at its first occurrence in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement, New Matter (New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15-16, 18-21 and 24-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventors, at the time the application was filed, had possession of the claimed invention.

In particular, the specification and claims as originally filed fail to provide adequate written description for the newly added limitation directed to "each dosage form releases a fixed ratio of isomer" as recited in instant claims 1 and 16.

MPEP §2163 states, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test of sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))…Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)."

Applicant references various portions of the instant specification as allegedly providing written support for this newly added limitation, e.g., p.5, l.13-15, 18-21, 25-33; p.6, l.11-13; p.7, l.11-21; and p.39, l.1-14.

However, while such portions of the instant specification have been fully and carefully

considered, the disclosure of the use of various dosage forms that each *contain a fixed ratio of isomer* fails to provide adequate written support to now narrow the claimed to read upon the use of various dosage forms that each *release a fixed ratio of isomer*. This is a concept that is not adequately supported by the written description of the invention as provided in the specification and claims as originally filed because the disclosure of amphetamine dosage forms that each contain a fixed isomer ratio (e.g., a fixed ratio of 3:1 d- to l-amphetamine) does not provide adequate support to then narrow the claims to read upon these same amphetamine dosage forms that each *release a fixed ratio of isomer*. This newly amended limitation represents a narrowing of the subject matter both claimed and disclosed in the specification and claims as originally filed that is not adequately supported, either explicitly or implicitly, by the original disclosure and clearly circumscribes a concept that was not in Applicant's possession at the time of the invention.

As stated in MPEP §2163, "The subject matter of the claim need not be described literally (i.e., using the same terms of *in haec verba*) in order for the disclosure to satisfy the description requirement." However, considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the concept of each dosage form releasing a fixed ratio of isomer (claims 1 and 16).

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 15-16, 18-21 and 24-29 are rejected under 35 U.S.C. 112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, there is insufficient antecedent basis for the limitation "the molar ratio" in lines 2-3 of instant claim 1 and again in lines 4-5 of instant claim 16, since the preceding text of the claims fails to set forth any reference to "a molar ratio" *per se*.

For these reason, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13, 15-16, 18-21 and 24-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patrick et al. ("Pharmacology of Methylphenidate, Amphetamine Enantiomers and Pemoline in Attention-Deficit Hyperactivity Disorder", 1997; p.527-546) in view of Hartmann et al. ("Sleep: Effects of d- and l-amphetamine in Man and in Rat; *Psychopharmacology*, 1976; p.171-175), Epstein et al. (WO

02/039998; May 23, 2002), Drug Facts and Comparisons (1996; p.1230-1233) and Remington's Pharmaceutical Sciences (Sixteenth Edition, 1980; p.1594-1602).

All references are already of record.

Patrick et al. teaches dextroamphetamine and levoamphetamine mixed salts, marketed and sold under the brand name ADDERALL for use in the treatment of attention-deficit hyperactivity disorder (ADHD; p.537, col.2, last 2 paragraphs). Patrick et al. discloses that ADDERALL is a combination product comprising dextroamphetamine saccharate, dextroamphetamine sulfate, racemic amphetamine aspartate and racemic amphetamine sulfate (p.537, col.2, last para.). Patrick et al. further teaches that the total free base equivalence in, for example, a 10 mg tablet is 6.3 mg, of which 81% is dextroamphetamine and 19% is levoamphetamine (i.e., which corresponds to 5.103 mg d-amphetamine and 1.197 mg l-amphetamine, which is a ratio of approximately 4.26:1 d-amphetamine to l-amphetamine as required by instant claims 3-4, 6, 20, 25 and 29; p.537, col.2, last para.). Patrick et al. also discloses that combination products of dextroamphetamine and levoamphetamine mixed salts, such as ADDERALL, were known and used in the art for the treatment of patients with ADHD (p.536-538). Patrick et al. states that ADDERALL was known to be comprised primarily of dextroamphetamine and exhibited similar side effects to that of dextroamphetamine alone (p.537, col.2, last para. and p.538, col.1, "Side-effects"), such as insomnia, anorexia, weight loss, irritability, abdominal pain or headache (p.537, col.1, para.3). While Patrick et al. states that dextroamphetamine produced more pronounced psychopharmacological effects that the (-)-isomer, he states that dextroamphetamine produced more pronounced peripheral sympathomimetic side-effects than levoamphetamine (p.536, col.2, para.1).

Patrick et al. fails to teach the administration of greater than one dosage form (i.e., two dosage forms as in instant claims 13, 20-21, 25 and 29), each releasing a fixed ratio of isomer, wherein the molar ratio of l-amphetamine to d-amphetamine released from the combination in a time period later in the day is higher than the ratio released therefrom in a time period earlier in the day (claims 1 and 16); wherein

the amphetamine released in the later period is, *inter alia*, a mixture of d- and l-amphetamine having more l- than d-amphetamine (claims 8-9) or is substantially only l-amphetamine (claim 11); wherein the molar ratio released of l- to d-amphetamine in said later period is greater than 1/1 or is l-isomer only (claims 20-21, 25-26 and 29) or is about 2/1 to about 6/1 (claim 10) or the total amount of l-isomer to the total amount of d-isomer administered per day is greater than 1:3 (claim 16); wherein the total amphetamine dose per day is about 1 to about 200 mg (claim 12); wherein said earlier period is the time before about 1:00 pm of a given day and said later period is the time thereafter (claim 2) or that the time period later in the day is at least about one hour following the time period earlier in the day (claim 16); the dosage forms are immediate, pulse, sustained or controlled release dosage forms (claims 18-19 or 24); or that the effectiveness of treatment of inattentiveness in an ADHD human patient later in the day by said l-isomer is as good as treatment with a corresponding molar amount of d-amphetamine but is accompanied by a lesser side effect of sleep deterioration and/or decreased food intake (claim 28).

Hartmann et al. teaches, "It is widely recognized that in general the amphetamines produce cortical arousal or activation and that they promote wakefulness in man at times of drowsiness or sleep deprivation. The dextro-isomer (d-amphetamine) has usually been found to be more potent in these regards than the levo-isomer (l-amphetamine)." (col.1, p.171, para.1 following abstract) Hartmann et al. further teaches that waking was increased by d-amphetamine but not by l-amphetamine in both humans and rats (col.1, p.172, para.1 following "Results").

Epstein et al. teaches that the (-)-isomer (i.e., levoamphetamine) showed more potent memory enhancing effects than the (+)-isomer (i.e., dextroamphetamine) and was also not found to be addictive. Epstein et al. teaches, "In particular, we describe herein the use of pharmaceutical preparations for increasing long-term potentiation and/or improving long-term memory in animals, such as humans, which include R-(-)-amphetamine or a derivative thereof. R-(-)-amphetamine is at least 4 times more effective as a memory enhancer as compared to the commonly prescribed S-(+)-enantiomer of amphetamine. In

addition, unlike S-(+)-amphetamine, the R-(-)-enantiomer has not been shown to be addictive." (p.26, l.26-32)

Drug Facts and Comparisons teaches various pharmaceutical therapies containing amphetamines, specifically, dextroamphetamine, and further teaches that such therapies should be administered early in the day to avoid nighttime insomnia and should be administered at the lowest effective dosage, which should be adjusted individually (p.1232). Drug Facts also teaches that the dosage of amphetamines will rarely exceed 40 mg/day (p.1233).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ a pharmaceutical combination regimen of at least two dosage forms to be administered during the day, wherein (1) d-isomer (i.e., either exclusively d-isomer or d-isomer in combination with l-isomer but wherein more d-isomer than l-isomer was present, such as the dosage form disclosed by Patrick et al.) was administered early in the day so as to obtain the therapeutic benefit of d-amphetamine (i.e., to promote wakefulness and alertness as evidenced by Hartmann et al.) while avoiding nighttime insomnia caused by said d-isomer when administered later in the day as evidenced by Drug Facts, and (2) l-isomer (i.e., either exclusively l-isomer or l-isomer in combination with d-isomer but wherein more l-isomer than d-isomer was present, such as, e.g., a molar ratio of greater than 1/1 or about 2/1 to about 6/1 as in instant claims 10, 20-21, 25-26 and 29, or that the total amount of l-isomer to total amount of d-isomer per day is greater than 1:3, since the administration of a second dosage form containing l-isomer in combination with the dosage form of Patrick et al., which has a 1/4.26 l:d isomer ratio, would result in a total amount of l-isomer to total amount of d-isomer administered per day to be greater than 1/3) was administered later in the day as to obtain the therapeutic benefit of l-amphetamine (i.e., to promote memory enhancement with less addictive properties as evidenced by Epstein et al.) while minimizing the effect on wakefulness (and, thus, the promotion of nighttime insomnia) as evidenced by Hartmann et al. Such a person would have been motivated to do so in order to maintain alertness, wakefulness, attention

and enhanced memory function during daytime hours (particularly morning and early afternoon, such as, e.g., before 1:00 pm as in instant claim 2 and/or wherein the time period later in the day is at least about one hour following the time period earlier in the day as in instant claim 16), when such characteristics would be necessary for a patient with ADHD to function during school, work, etc., while minimizing the disruptive effect of amphetamine stimulant therapy on sleep patterns (i.e., via causing nighttime insomnia).

Moreover, such a combination of dosage forms would have been reasonably expected to result in a therapeutic regimen that was at least equivalent to the efficacy demonstrated by a corresponding molar amount of d-amphetamine (as recited in instant claim 28) because said combination would have caused fewer adverse effects on sleep patterns (i.e., by minimizing nighttime insomnia) via the administration of l-isomer, which is known to minimize the effect on wakefulness as taught by Hartmann et al., and, as evidenced by Patrick et al., the administration of l-isomer was known to result in fewer side effects than the d-isomer, which is known to cause anorexia and weight loss (p.536, col.2, para.1).

Regarding the use of various dosage forms with immediate, pulsed, controlled or sustained release (claims 18-19 and 24), Remington's Pharmaceutical Sciences teaches that various methods of release were known in the art at the time of the invention and include, *inter alia*, immediate, pulsed, controlled or sustained release formulations (p.1594-1602). The use of any one or more of these specific types of release formulations would have been well within the purview of, and *prima facie* obvious to, one of ordinary skill in the art at the time of the invention motivated by the desire to provide an optimal combination regimen to balance the therapeutic effects while minimizing adverse effects and obtaining release of the active agents consistent with said balance.

Regarding the use of a total amphetamine dose per day of about 1 to about 200 mg (claim 12), one of ordinary skill in the art would have found it *prima facie* obvious to use a dose within the claimed range because, as evidenced by Drug Facts, the total daily dose of amphetamine generally should not

exceed 40 mg/day and should be adjusted per individual needs. Furthermore, the determination of the optimum total dosage per day, as well as the optimum molar ratios of d- to l-isomer, by which to treat ADHD with the presently claimed pharmaceutical combination would have been a matter well within the purview of, and *prima facie* obvious to, one of ordinary skill in the art at the time of the invention. Factors to be considered in making such a determination would have included, *inter alia*, age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound(s) employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination, etc. Thus, the total dosage amount per day and the molar ratios that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, are not seen to be inconsistent with those that would have been routinely determined by the skilled artisan.

Conclusion

Rejection of claims 1-13, 15-16, 18-21 and 24-29 remains proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

April 23, 2009

/Ardin Marschel/
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